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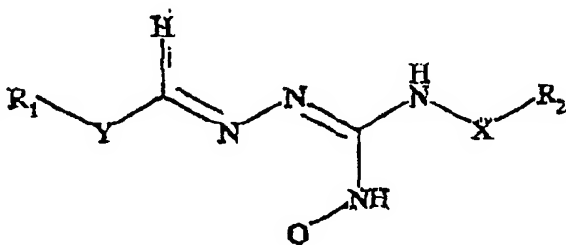
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(54) Title: COMPOUNDS ACTING AS MELANOCORTIN RECEPTOR LIGANDS



(I)

(57) Abstract: The present invention provides novel com-  
pounds and use of compounds of general formula (I) as lig-  
ands to the melanocortin receptors and/or for treatment of  
disorders in the melanocortin system: Wherein X and Y are  
independently chosen from O, N, S and (CH<sub>2</sub>)<sub>n</sub>, where n is  
0, 1, 2, 3, 4 or 5, or a combination of these and may con-  
tain carbon-carbon multiple bonds and branched chains as  
well as alicyclic and heterocyclic groups; Q is H or OH; R<sub>1</sub>  
and R<sub>2</sub> can be either the same or different and are chosen  
from hydrogen or the residue of an aromatic group as listed

in Scheme 1 and the pharmacologically active salts thereof.

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## COMPOUNDS ACTING AS MELANOCORTIN RECEPTOR LIGANDS

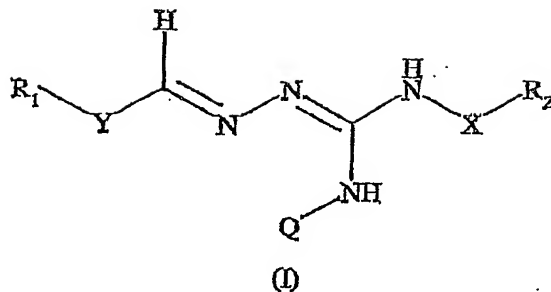
The present invention relates to novel guanidines and to the use of guanidines for the treatment of obesity, anorexia, inflammation, mental disorders and other diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

A number of large linear and cyclic peptides are known in the art which show high specific binding to melanocortin (MC) receptors. The agonistic and/or antagonistic properties of these peptides are also known. See for example "Melanocortin Receptor ligands and methods of using same" by Dooley, Girtten and Houghten (WO 99/21571). There remains, however, a need to provide low molecular weight compounds showing agonistic or antagonistic properties to the melanocortin receptors.

A number of low molecular weight compounds are known, e.g. isoquinolines, spiropyridines and benzimidazoles, which show activity on the MC- receptors. See "Isoquinoline compound melanocortin receptor ligands and methods of using same" by Basu *et al*, Trega Biosciences Inc. (PCT/US99/09216), "Spiropiperidine derivatives as melanocortin receptor agonists" by Nargund, Ye, Palucki, Bakshi, Patchett and van der Ploeg (PCT/US99/13252) and "Melanocortin receptor-3 ligands to treat sexual dysfunction" by Dines *et al* (WO 01/05401). The compounds in the present invention are structurally different from the above mentioned compounds and, consequently, constitute a new class of compounds that show activity to the MC-receptors.

One aspect of the present invention is therefore to provide low molecular weight compounds showing activity on melanocortin receptors and which may be taken up after per oral administration and which may penetrate well through the blood brain barrier.

The present invention provides novel compounds within and the use of compounds of general formula (I) and their tautomeric forms:



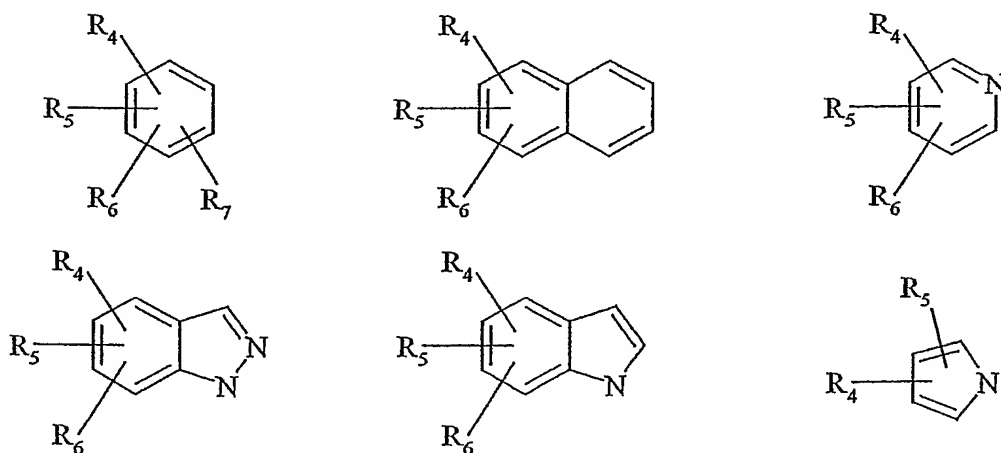
- 5 wherein X and Y are independently chosen from O, N, S and  $(CH_2)_n$  where  $n$  is 0, 1, 2, 3, 4 or 5, or a combination of these and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups.

Q is H or OH;

10

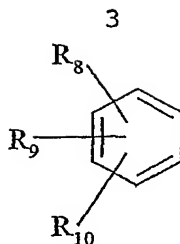
$R_1$  and  $R_2$  can be either the same or different and are chosen from hydrogen or the residue of an aromatic group as listed in Scheme 1:

Scheme 1



15

- wherein  $R_4$ ,  $R_5$ ,  $R_6$  and  $R_7$  are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho, or from;
- 20



wherein  $R_8$ ,  $R_9$  and  $R_{10}$  are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho;  
 5 with the proviso that where X is  $(CH_2)_n$  and n is O,  $R_2$  is not H;  
 and the pharmacologically active salts thereof.

10 When used in the foregoing definitions, the term alkyl is meant to include straight or branched chain hydrocarbon groups as well as alicyclic and fused alicyclic groups; and the term alkoxy is meant to include straight or branched chain alkoxy groups.

The term halogen includes fluoro, chloro, bromo and iodo.

15

Preferably, the "alkyl having 1 to 8 carbon atoms" is a lower alkyl such as methyl, ethyl, propyl or iso-propyl.

Preferably, the "alkoxy having 1 to 5 carbon atoms" is a lower alkoxy such as methoxy,  
 20 ethoxy, propoxy or iso-propoxy.

Preferably, the trifluoroalkyl is trifluoromethyl, trifluoroethyl, trifluoropropyl or trifluoroiso-propyl.

25 X and Y may also be NH or N-alkyl, preferably N-methyl or N-ethyl.

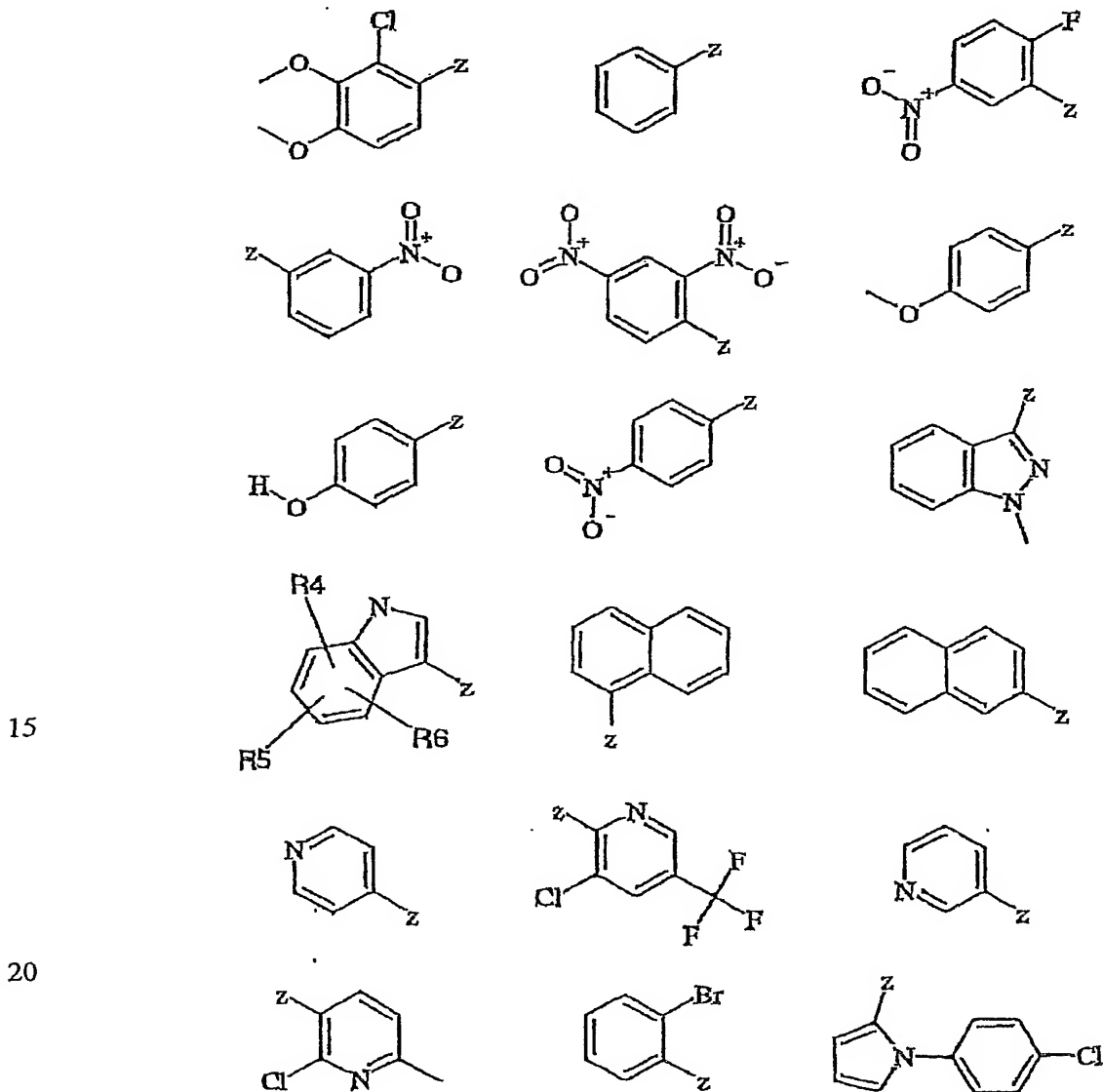
When X represents  $(CH_2)_n$ , n is preferably 1 or 2.

When Y represents  $(CH_2)_n$ , n is preferably 0, 1 or 2.

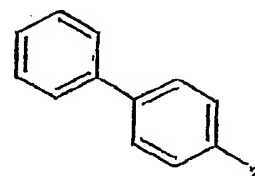
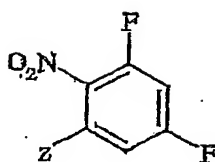
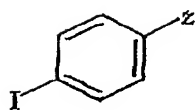
In cases where  $R_1$  and/or  $R_2$  are chosen from the compounds given in Scheme 1 and the compound is a bicyclic or tricyclic ring, it should be noted that the  $R_4$ - $R_7$  substituents may be present on any of the rings.

- 5 Furthermore, it should be noted that the Scheme 1 compounds may be attached to the carbon backbone of the compound of general Formula (I) at any suitable point within the compound of Scheme 1, preferably at the 1, 2 or 3 position.

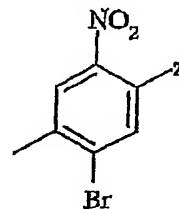
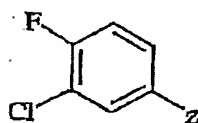
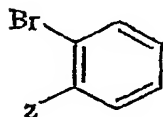
10 Examples of novel compounds which comprise a further feature of the present invention are those wherein  $R_1$  and  $R_2$  are selected from;



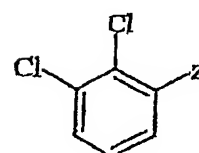
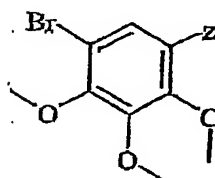
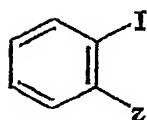
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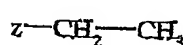
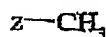
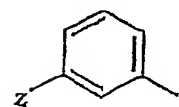
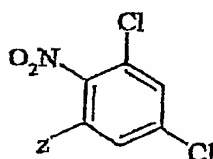
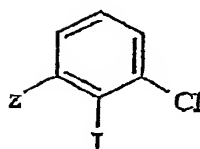
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15



20 wherein *z* denotes the point of attachment;  
with the proviso that:

when *R*<sub>1</sub> is phenyl, *R*<sub>2</sub> must be selected from a different substituent than phenyl;

when *R*<sub>1</sub> is 4-methoxyphenyl, *R*<sub>2</sub> must be selected from a different substituent than 4-methoxyphenyl or 1,3-dinitrophenyl;

25 when *R*<sub>2</sub> is 4-methoxyphenyl, *R*<sub>1</sub> must be selected from a different substituent than 4-methoxyphenyl; and

when *R*<sub>2</sub> is methyl, *R*<sub>1</sub> must be selected from a substituent different than phenyl.

30 The compounds of Formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with appropriate physiologically acceptable acids, e.g. inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, succinic, fumaric, tartaric, citric, pantoic, oxalic and *para*-toluenesulphonic acid.

Conversely, the salt form may be converted into the free base form by treatment with alkali.

The present invention relates to novel guanidines. Compounds of the present invention have  
5 been biologically tested in the melanocortin system and have surprisingly been shown to be capable of binding to melanocortin receptors as well as showing activity in functional assays.

Compounds of the present invention are either agonists or antagonists of a specific MC-receptor or of a number of MC-receptors, e.g. MC1, MC3, MC4 or/and MC5 receptors.

10

The MC-receptors belong to the class of G-protein coupled receptors which are all built from a single polypeptide forming 7 transmembrane domains. Five such receptors types, termed MC1, MC2, MC3, MC4 and MC5, have been described. The MC receptor's signaling is mainly mediated via cAMP but also other signal transduction pathways are known. They are  
15 distinctly distributed in the body.

MC-receptors are linked to a variety of physiological actions that are thought to be mediated by distinct subtypes of the MC-receptors. In many cases, however, it is not entirely clear which of the subtypes is responsible for the effect.

20

It has long been known that MSH-peptides may affect many different processes such as motivation, learning, memory, behaviour (including feeding and sexual), inflammation (including immunostimulatory and immunosuppressive), body temperature, pain perception, blood pressure, heart rate, vascular tone, brain blood flow, trophic effects in different organs,  
25 nerve growth, placental development, endocrine and exocrine functions, aldosterone synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, effects on other organs, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, intrauterine foetal growth, as well as other events surrounding parturition and natriuresis (Eberle, AN: The melanotropins: Chemistry, physiology and mechanisms of  
30 action. Basel: Karger, Switzerland. 1988, ISBN 3-8055-4678-5; Gruber, and Callahan, Am. J. Physiol. 1989, 257, R681-R694; De Wildt *et al.*, J. Cardiovascular Pharmacology. 1995, 25, 898-905), as well as inducing natriuresis (Lin *et al.*, Hypertension. 1987, 10, 619-627).

It is also well-known that the immunomodulatory action of  $\alpha$ -MSH includes both immuno-stimulatory and immunosuppressive effects. Several studies have shown that  $\alpha$ -MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 and TNF $\alpha$ , and induces the production of the anti-inflammatory cytokine, IL-10 (for review see Catania  
5 & Lipton, 1993).

Eating behaviour is regulated by a complex network of physiological regulatory pathways that involve both the central nervous system and peripheral sites. Factors such as leptin, insulin, NPY (neuropeptide Y), orexins, CRF (Corticotropin-Releasing Factor, release hormone) and  
10 melanocortic peptides (Schwartz; Nature Medicine 1998, 4, 385-386) are known to control the amount of food intake both during short and long term, which may affect body weight, body fat mass and growth rate. Recent studies have shown a role of MC-receptors, especially the MC4 receptor, for control of food intake, and there is evidence indicating that the melanocortins and the MC4 receptor are important factors downstream of leptin.  
15 Intracerebroventricular injections of the melanocortic peptides  $\alpha$ -MSH and ACTH(1-24) have been shown to markedly inhibit feeding (Poggioli *et al.*, Peptides, 1986, 7, 843-848; Vergoni *et al.*, Neuropeptides, 1986, 7, 153-158).

The MC5-receptor has recently been attributed a role in control of exocrine gland function  
20 (van der Kraan, *et al.*, Endocrinol. 1998, 139, 2348-2355; Chen *et al.*, Cell. 1997, 91, 789-798).

In addition, the melanocortic peptides have distinct effects on sexual functions in that they cause erection in males (Donovan, Psychol. Med. 1978, 8, 305-316), presumably mediated by  
25 a central agonistic effect of the peptide on MC-receptors. It has also been shown that a MC-receptor blocker could inhibit the erectogenic effect of melanocortic peptides (Vergoni *et al.*, Eur. J. Pharmacol, 1998, 362; 95-101).

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have  
30 valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression, anxiety, senile dementia, Alzheimer's disease, drug abuse disorders and eating disorders such as anorexia and bulimia.



Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of dysfunctions of the endocrine system and other hormonal systems such as excessive menstruations, endometriosis, events related to parturition, dysfunctions related to prolactin, dysfunctions  
5 related to growth hormone, dysfunctions related to testosterone, dysfunctions related to estrogen, dysfunctions related to glucocorticoids, dysfunctions related to luteinizing hormone and follicle stimulating hormone, inducing abortion, for prevention of abortion and/or for treatment of events related to parturition.

10 Compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of sexual functions / dysfunctions such as inducing erection in man, to induce erection in animal breeding, to stimulate intercourse in animals which are difficult to mate, in particular rare species or valuable strains, pets, cats, dogs, horses or to reduce sexual behaviour in animals, e.g. for  
15 pets, cats etc., to treat impotence and disorders related to sexual drive, including lack of sexual drive or abnormal sexual drive in both men and women.

Compounds of Formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of inflammation such as  
20 inflammations related to the production of nitric oxide, inflammation related to increased amounts (upregulated amounts) of inducible nitric oxide synthase, inflammation related to activation of transcriptional activators, inflammation related to nuclear factor kappa beta, inflammation related to macrophages, neutrophils, monocytes, keratinocytes, fibroblasts, melanocytes, pigment cells and endothelial cells, inflammation related to increased  
25 production and/or release of inflammatory cytokines, such as e.g. interleukins, in particular interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ).

In the present specification, "increased production" refers to increased formation, increased release, or increased amount of an endogenous compound locally, regionally or systemically  
30 in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "upregulated" refers to an increased activity or amount of the compound compared with that in a healthy individual.

In the present specification, "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "downregulated" refers to a decreased activity or amount of the compound compared with  
5 that in a healthy individual.

In particular, positive treatment effects or preventive effects may be seen in conditions where inflammation or an inflammatory-like condition is caused by or being associated with one or more of the following: allergy, hypersensitivity, bacterial infection, viral infection,  
10 inflammation caused by toxic agent, fever, autoimmune disease, radiation damage by any source including UV-radiation, X-ray radiation,  $\gamma$ -radiation,  $\alpha$ - or  $\beta$ -particles, sun burns, elevated temperature or mechanical injury. Moreover, inflammation due to hypoxia, which is optionally followed by reoxygenation of the hypoxic area, is typically followed by severe inflammation, which condition may be positively affected by treatment with a compound of  
15 the invention.

In very specific embodiments of the invention, a compound of the invention may be administered for the prevention or therapeutic treatment of inflammatory diseases of the skin (including the dermis and epidermis) of any origin, including skin diseases having an  
20 inflammatory component. Specific examples of this embodiment of the invention include treatment of contact dermatitis of the skin, sunburns of the skin, burns of any cause, and inflammation of the skin caused by chemical agents, psoriasis, vasculitis, pyoderma gangrenosum, discoid lupus erythematosus, eczema, pustulosis palmo-plantaris, and phemphigus vulgaris.

25

Also comprised by the invention is the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of an inflammatory disease in the abdomen, including an abdominal disease having an inflammatory component. Specific examples of the treatment of such a disease with a compound of the invention are gastritis,  
30 including one of unknown origin, gastritis perniciosa (atrophic gastritis), ulcerous colitis (colitis ulcerosa), morbus Crohn, systemic sclerosis, ulcus duodeni, coeliac disease, oesophagitis and ulcus ventriculi.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of systemic or general and/or local immunological diseases, including those of an autoimmune nature, and other inflammatory diseases of a general nature. Specific examples include treatment of rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, polymyalgia rheumatica, Wegener's granulomatosis, sarcoidosis, eosinophilic fasciitis, reactive arthritis, Bechterew's disease, systemic lupus erythematosus, arteritis temporalis, Behcet's disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

10

Further included in the invention is administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of a disease of the peripheral and/or central nervous system related to inflammation. Included in this aspect of the invention is the treatment of cerebral vasculitis, multiple sclerosis, autoimmune ophthalmitis and polyneuropathia. Comprised by the invention is also the administration of a compound of the invention for the treatment of an inflammation of the central nervous system to prevent apoptotic cell death. Moreover, as some of the compounds of the invention show a distinct ability to induce nerve regeneration, positive treatment effects are often seen in central nervous system diseases involving damage of cells in this region. This aspect of the invention also includes treatment of traumatic injuries to the central nervous system, brain edema, multiple sclerosis, Alzheimer's disease, bacterial and viral infections in the central nervous system, stroke, and haemorrhagia in the central nervous system.

20

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, Sjögren's syndrome, episcleritis, scleritis, sarcoidosis affecting the eye and polychondritis affecting the eye.

30

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the ear related to inflammation, specific examples of which include polychondritis affecting the ear and external otitis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the nose related to inflammation, specific examples of which are sarcoidosis, polychondritis and mid-line granuloma of the nose.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the mouth, pharynx and salivary glands. Specific examples include Wegener's granulomatosis, mid-line granuloma, Sjögren's syndrome and polychondritis in these areas.

Included in the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation in the lung. Specific examples include treatment of idiopathic alveolitis, primary pulmonary hypertension, bronchitis, chronic bronchitis, sarcoidosis, alveolitis in inflammatory systemic disease, pulmonary hypertension in inflammatory systemic disease, Wegener's granulomatosis and Good Pastures' syndrome.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the heart. Specific examples include treatment of pericarditis, idiopathic pericarditis, myocarditis, Takayasu's arteritis, Kawasaki's disease, coronary artery vasculitis, pericarditis in inflammatory systemic disease, myocarditis in inflammatory systemic disease, endocarditis and endocarditis in inflammatory systemic disease.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the liver. Specific examples include treatment of hepatitis, chronic active hepatitis, biliary cirrhosis, hepatic damage by toxic agents, interferon induced hepatitis, hepatitis induced by viral infection, liver damage induced by anoxia and liver damage caused by mechanical trauma.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation

of the pancreas. Specific examples include treatment (and prevention) of diabetes mellitus, acute pancreatitis and chronic pancreatitis.

Comprised by the invention is also the administration of a compound of formula (I) or a  
5 pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the thyroidea. Specific examples of these embodiments of the invention include treatment of thyroiditis, autoimmune thyroiditis and Hashimoto's thyroiditis.

Comprised by the invention is also the administration of a compound of formula (I) or a  
10 pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the kidney. Specific examples include treatment of glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLAB27 associated diseases, IgA nephritis (IgA = Immunoglobulin A), pyelonephritis, chronic pyelonephritis and interstitial nephritis.

15 Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the joints. Specific examples include treatment of Bechterew's disease, psoriatic arthritis, rheumatoid arthritis, arthritis in colitis ulcerosa, arthritis in morbus Crohn,  
20 affection of joints in systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, reactive arthritis, Reiter's syndrome. Moreover, included in this embodiment of the invention is treatment of arthrosis of any joint, in particular arthrosis of finger joints, the knee and the hip.

25 Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of blood vessels. Specific examples include treatment of arteritis temporalis, periarteritis nodosa, arteriosclerosis, Takayasu's arteritis and Kawasaki's disease. Particularly advantageous is the capacity of some compounds of the invention to afford protection against  
30 and prevention of arteriosclerosis. This is in part due to the capacity of some compounds of Formula (I) or the pharmacologically acceptable salts thereof to prevent the induction of inducible nitric oxide synthesis (iNOS) caused by the action of oxidized Low Density Lipoprotein on endothelial cells and blood vessel walls.

Comprised by the invention is also the administration of a compound of the invention for the treatment of drug-induced disorders of the blood and lymphoid system, including the treatment of drug-induced hypersensitivity (including drug hypersensitivity) affecting blood cells and blood cell forming organs (e.g. bone marrow and lymphoid tissue). Specific  
5 embodiments of this aspect of the invention include the treatment of anemia, granulocytopenia, thrombocytopenia, leukopenia, aplastic anemia, autoimmune hemolytic anemia, autoimmune thrombocytopenia and autoimmune granulocytopenia.

The compounds of the invention may also be administered for the treatment of fast allergic  
10 disorders (Type I allergy). Included in this embodiment of the invention is the treatment of anaphylactic reactions, anaphylactoid reactions, asthma, asthma of allergic type, asthma of unknown origin, rhinitis, hay fever and pollen allergy.

Comprised by the invention is also the administration of a compound of formula (I) or a  
15 pharmacologically acceptable salt thereof for the treatment of inflammation related to infections of any origin. Specific examples include treatment of inflammation secondary to infection caused by virus, bacteria, helminths and protozoae.

Comprised by the invention is also the administration of a compound of formula (I) or a  
20 pharmacologically acceptable salt thereof for the treatment of inflammations related to trauma and/or tissue injury of any origin.

Compounds of formula (I) or pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of disorders of the  
25 cardiovascular system such as disorders related to blood pressure, heart rate, vascular tone, natriuresis, bleeding, shock, disorders related to ischemia, infarction, reperfusion injuries, arrhythmias of the heart, in particular during ischemia, or for the treatment of arrhythmias associated with reoxygenation of a previously ischemic period of the heart.

30 Compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of pain such as pain of central origin, pain seen after damage to the CNS, stroke, infarction, pain of peripheral origin, chronic pain, neuropathies and disorders where a treatment effect is achieved by stimulation of receptors in the periaqueductal grey area.

Because of the capacity of compounds of the invention to stimulate pigment formation in epidermal cells, compounds of the invention may be also useful for inducing skin tanning for cosmetic reasons, for treatment of vitiligo, or any other condition where darkening of skin color is desired. Moreover, because of the ability of some of the compounds of the invention to inhibit pigment formation in cells of the skin, they may also be useful for inducing lighter skin color for cosmetic reasons, or during any condition where a lighter color of skin is desired.

Compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful to cause skin tanning, darkening the colour of the skin, to induce melanin synthesis in the skin, to reduce skin tanning, lightening the colour of the skin, to reduce or block melanin synthesis in the skin, to cause anti-inflammatory actions in the skin, to modulate epidermal growth, to improve wound healing, to treat acne, seborrhoea, acne roseacea, conditions related to malfunctions of the glands of the skin, e.g. sebaceous glands and over or underproduction of sebum.

Compounds of the invention are useful for inhibiting or stimulating the *in vivo* formation of second messenger elements such as cAMP. Such inhibition/stimulation may be used in cells or crushed cell systems *in vitro*, e.g. for analytical or diagnostic purposes.

For analytical and diagnostic purposes the compounds of the invention may be used in radioactive form where they comprise one or more radioactive labels or gamma or positron emitting isotopes, to be used in radioligand binding for the quantification as well as tissue localisation of MC-receptors, for analysis of dissociation/association constants, and for imaging of *in vivo* binding by the use of scintigraphy, positron emission tomography (PET) or single photon emission computed tomography (SPECT), or for the diagnosis of disease and treatment of any malignancy where the malignant cells contain MC receptors.

Alternatively the compounds of the invention can be labelled with any other type of label that allows detection of the respective compound, e.g. fluorescence, biotin, NMR, MRI, or labels activated by gamma-irradiation, light photons or biochemical processes, or by light or UV-light (the latter in order to obtain a compound useful for covalent labelling of MC receptors by a photoaffinity technique).

Compounds of formula (I) or the pharmacologically acceptable salts thereof may also be tagged with a toxic agent (i.e. doxorubicin, ricin, diphtheria toxin or other) and used for targeted delivery to malignant cells bearing MC receptors, or tagged with a compound  
5 capable of activating the endogenous immune system for triggering the immune system (for example a compound, monoclonal antibody or other, capable of binding to a T-cell antigen, e.g. CD3 or other) for treatment of malignancies and other MC receptor expressing diseases. The thus formed hybrid compound will direct cytotoxic cells to the malignant melanoma cells or the MC1-receptor bearing malignant cells and inhibit the tumor growth.

10

Compounds of formula (I) or a pharmacologically acceptable salt thereof may be attached to the antibody chemically by covalent or non-covalent bond(s).

15

Compounds of the invention may be used for the treatment and diagnosis of diseases, disorders and/or pathological conditions in an animal, in particular in man.

20

The present invention also relates to a pro-drug which, upon administration to an animal or a human, is converted to a compound of the invention. Pro-drugs of the compounds of formula (I) and their pharmacologically acceptable salts may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below.

25

The compounds of the present invention may be bound covalently or non-covalently to one or several of other molecule(s) of any desired structure(s); the thus formed modified compound or complex may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below. In a particularly important embodiment of the invention, a radioactively-labelled molecule is covalently bound to a compound of formula (I) or a pharmacologically acceptable salt thereof so as to make a compound of formula (I) or a pharmacologically acceptable salt thereof  
30 radioactively labelled.

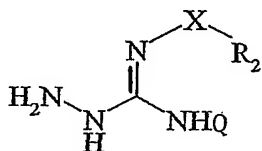
The invention also relates to methods for the manufacture of and pharmaceutical preparations comprising one or more of the compounds of the invention, as well as to their uses for various medical and veterinary practices related to melanocyte stimulating hormone receptors.



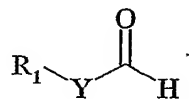
Compounds of the invention have an effect on xanthine oxidase in mammals, including man.

## METHODS OF PREPARATION

Compounds of the invention may be prepared as follows:



II

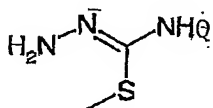


III

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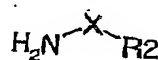
A guanidine derivative, II, is reacted with the appropriate aldehyde, III, resulting in the formation of a compound of the general Formula (I). X, Y, Q, R<sub>1</sub> and R<sub>2</sub> are as previously defined. Any of derivatisation, protection, deprotection and activation steps are used if necessary. If necessary, guanidine derivative II may be prepared by reacting a thiosemicarbazide (IV) with an amine (V):

10



IV

15



V

20

## EXAMPLES

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for the intended purposes. The preparation of the compounds of general formula (I) is given schematically in Example 1 below. Specific synthetic procedures are given in methods 1 and 2. The compounds are numbered and are listed with their complete name below.

30

Method 1Preparation of Compound 1, N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine

- 5 536 mg (5 mmol) benzylamine and 1.17 g (5 mmol) S'-methylthiosemicarbazide hydroiodide was mixed in 10 ml of ethanol. The reaction mixture was refluxed for 5 minutes after which it was cooled down to room temperature and the residue filtered off. The crude product of N-amino-N'-benzylguanidine was reacted with 1.0 g (5 mmol) 2-chloro-3,4-dimethoxybenzaldehyde under reflux for 5h, after which the solvent was removed under vacuum to give a white solid. The product was obtained by recrystallisation from methanol.
- 10 Yield of title compound 1 was 1.65 g (77%). M.p. 223-225°C.

Method 2Preparation of Compound 2, N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-phenylguanidine

- 15 0.22 g (1.1 mmol) 2-chloro-3,4-dimethoxybenzaldehyde and 0.34 g (1 mmol) N-hydroxy-N'-phenylaminoguanidine tosylate was mixed in 7 ml methanol. The reaction mixture was refluxed for 80 min after which it was cooled down to room temperature. The solvent was evaporated and 10 ml acetonitrile was added and the solution was stirred for 1 h. The precipitate formed was filtered, washed with ether and subsequently dried. The yield of title compound 2 was 0.40 g (77%) as a crystalline solid. M.p. 167-169°C.

20

Compounds 3 – 83 were prepared in an analogous manner:

Compounds 1-83

No.	Name	Melting point (°C)
1	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine	215-217
2	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-phenylguanidine	167-168.5
3	N-(2-Fluoro-5-Nitrobenzylideneamino) N'-hydroxy-N''-phenylguanidine	95-97

4	N-(3-nitrobenzylideneamino)-N'-hydroxy-N''-phenylguanidine	152-153.5
5	N-(2,4-dinitrobenzylideneamino)-N'-hydroxy-N'''-phenylguanidine	145-148
6	N-(2-fluoro-5-nitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine	181-183
7	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-methylguanidine	180-181.5
8	N-(3-nitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine	192.5-194
9	N-(2,4-dinitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine	221-222
10	N-(4-methoxybenzylideneamino)-N'-(2-phenylethyl)guanidine	126-128
11	N-(pyrid-4-yl-methylideneamino)-N'-(naphthalen-1-yl-methyl)guanidine	260-262
12	N-(1H-indol-3-ylmethylideneamino)-N'-(2-phenylethyl)guanidine	207-209
13	N-(1H-indol-3-yl-methylideneamino)-N-(naphthalen-1-ylmethyl)guanidine	213-215
14	N,N'-bis[1H-indol-3-yl-methylideneamino]guanidine	296-298
15	N-(pyrid-4-yl-methylideneamino)-N'-[2-(1H-indol-3-yl-ethyl)]guanidine	121-123
16	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-phenylguanidine	179-181
17	N-(2-fluoro-5-nitrobenzylideneamino)-N'-phenylguanidine	191-193
18	N-(4-hydroxybenzylideneamino)-N'-benzylguanidine	192-194
19	N-(2,4-dinitrobenzylideneamino)-N'-phenylguanidine	180-190
20	N-(4-nitrobenzylideneamino)-N'-(2-phenylethyl)guanidine	241-243
21	N-(naphthalen-2-yl-methylideneamino)-N'-(2-phenylethyl)guanidine	244-246
22	N-(naphthalen-2-yl-methylideneamino)-N'-benzylguanidine	242-244
23	N-(naphthalen-2-yl-methylideneamino)-N'-naphthalen-2-ylguanidine	218-220
24	N-(4-Nitrobenzylideneamino)-N'-benzylguanidine	239-241
25	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(pyrid-3-ylmethyl)guanidine	58-60
26	N-(2-chloro-6-methyl-pyrid-3-ylmethylideneamino)-N'-(pyrid-3-ylmethyl)guanidine	227-228
27	N-(2-Bromobenzylideneamino)-N'-phenethylguanidine	154-155
28	N-(2-Bromobenzylideneamino)-N'-phenylguanidine	149-152
29	N-[1-(4-Chlorophenyl) 1H-Pyrrol-2-ylmethyleneamino]-N'-benzylguanidine	190-192
30	N,N'-Di-(naphthalen-1-ylmethyleneamino)guanidine	253-255
31	N,N'-Di-(2-Bromobenzylideneamino)guanidine	268-270
32	N,N'-Di-(2-Chloro-3,4-Dimethoxybenzylideneamino)guanidine	228-230
33	(3-Phenyl-allylideneamino)-N'-2-phenylethyl)guanidine	175-177
34	N,N'-Di-(1-(4-Chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine	221-223
35	N-(2-Fluoro-5-nitrobenzylideneamino)-N'-methylguanidine	217-219
36	N-(Indol-3-ylmethylenimino)-N'-(1-methylindazol-3-ylmethyl)guanidine	foam
37	N-(2-Chloro-3,4-dimethoxybenzylideneamino)-N'-methylguanidine	207-210

38	N-(indol-3-ylethylideneamino)-N'-(indol-3-ylethyl) guanidine	
39	N-(indol-3-ylmethylideneamino)-N'-indol-3-ylguanidine	
40	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N'-(N'-methyl-2-azaindol-3-yl-methyl)guanidine	
41	N-(indol-3-yl-methylideneamino)-N'-(N'-methyl-2-azaindol-3-yl-methyl)guanidine	
42	N-(indol-3-yl-butylideneamino)-N'-(N'-methyl-2-azaindol-3-yl-methyl)guanidine	
43	N-(1-methyl-indol-3-yl-methylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
44	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
45	N-(indol-3-ylmethylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
46	N-(indol-3-ylbutylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
47	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N'-(indol-3-ylmethyl) guanidine	
48	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N'-(indol-3-ylmethyl)guanidine	
49	N-(indol-3-ylmethylideneamino)-N'-(indol-3-ylmethyl) guanidine	
50	N-(indol-3-ylbutylideneamino)-N'-(indol-3-ylmethyl) guanidine	
51	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
52	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
53	N-(indol-3-ylmethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
54	N-(indol-3-ylbutylideneamino)-N'-(indol-3-ylbutyl) guanidine	
55	N-(2-methyl-indol-3-ylethylideneamino)-N'-(2-methyl-indol-3-ylethyl)guanidine	
56	N-(pyrid-3-ylpropylideneamino)-N'-(pyrid-3-ylpropyl) guanidine	
62	N-(pyrid-3-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl)guanidine	
64	N-(2-chloro-6-methyl-pyrid-3-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
65	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
66	N-(pyrid-3-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethyl) guanidine	
68	N-(3-chloro-5-methyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
69	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
70	N-(2-ethoxy-pyrid-3-ylmethylideneamino)-N'-(2-ethoxy-pyrid-3-ylmethyl)guanidine	
71	N-(pyrrol-2-ylmethylideneamino)-N'-(pyrrol-2-ylmethyl) Guanidine	
72	N-(3-nitrobenzylideneamino)-N'-phenylguanidine	
73	N-(3-nitrobenzylideneamino)-N'-methylguanidine	
74	N-(2,4-dinitrobenzylideneamino)-N'-methylguanidine	

75	N-(3,5-Difluoro-2-nitrobenzylideneamino)-N'-(4-Iodobenzyl)guanidine	
76	N-2-Bromobenzylideneamino)-N'-[2-(4-Biphenyl)-Ethyl]guanidine	
77	N-(3-Chloro-4-Fluorobenzylideneamino)-N'-[2-(3-Chloro-4-Fluorophenyl)ethyl]guanidine	
78	N-(4-Phenylbenzylideneamino)-N'-(5-Bromo-4-Methyl-2-Nitrobenzyl)guanidine	
79	N-(4-Phenylbenzylideneamino)-N'-(2-[2-Iodophenyl)ethyl]guanidine	
80	N-(3-Chloro-4-fluorobenzylideneamino)-N'-(2,3,4-trimethoxy-5-bromobenzyl)guanidine	-
81	N-(3-Chloro-2-iodobenzylideneamino)-N'-(2,3-Dichlorobenzyl)guanidine	
82	N-(3,5-Dichloro-2-nitrobenzylideneamino)-N'-[2-(3,5-difluoro-2-nitrophenyl)ethyl]guanidine	
83	N-(3-Iodobenzylideneamino)-N'-[2-(3-chloro-2-iodophenyl)ethyl]guanidine	

### Example 2

This example illustrates the potency of some of the compounds of formula (I) and their therapeutically active acid addition salts for treatment of mental disorders.

#### Test 1. Affinity for the MC1-receptor

- 5 The binding assay was carried out essentially as described by Lunec *et al*, Melanoma Res 1992; 2; 5-12 using  $I^{125}$ -NDP- $\alpha$ MSH as ligand.

#### Test 2. Affinity for the MC3-receptors, the MC4-receptors and the MC5-receptors

- The binding assays were carried out essentially as described by Szardenings *et al*, J Biol Chem 1997; 272; 27943-27948 and Schiöth *et al*, FEBS Lett 1997; 410; 223-228 using I125-  
10 NDP- $\alpha$ MSH as ligand.

#### Test 3. cAMP

The stimulation of cAMP was carried out essentially as described by Schiöth *et al*, Br J Pharmacol 1998; 124; 75-82, however, the response is given relative to  $\alpha$ -MSH.

Table 1. Affinity for MC-receptors

Compound	K <sub>i</sub> (μM)			
	MC1	MC3	MC4	MC5
27	1.24	7.96	1.35	5.80
29	3.12		0.61	1.32
33	1.32	5.36	3.59	8.23

5

Table 1b Influence on cAMP

Compound	cAMP agonist/plateau stim. α-MSH (%)		
	MC1	MC3	MC4
27	12	9	97
29	10	3	111
33	8	4	161

**EXAMPLE 3**

The following formulations are representative for all of the pharmacologically active compounds of the invention

10 Example of a preparation comprising a capsule

	Per capsule
Active ingredient, as salt	5 mg
Lactose	250 mg
Starch	120 mg
Magnesium stearate	5 mg
Total	380 mg

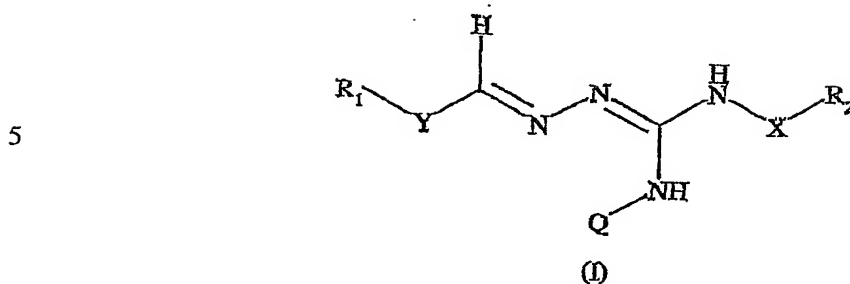
In case of higher amounts of active ingredient, the amount of lactose used may be reduced.

Example of a suitable tablet formulation.

	<b>Per tablet</b>
Active ingredient, as salt	5 mg
Potato starch	90 mg
Colloidal Silica	10 mg
Talc	20 mg
Magnesium stearate	2 mg
5 % aqueous solution of gelatine	25 mg
Total	152 mg

**Claims:**

1. The use of a compound of general formula (I)



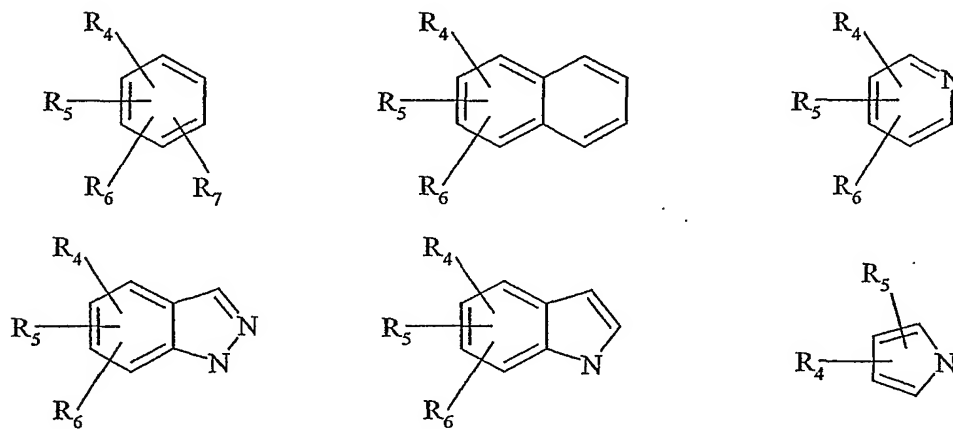
10 wherein

X and Y are independently chosen from O, N, S and  $(CH_2)_n$  where  $n$  is 0, 1, 2, 3, 4 or 5 or a combination of these and may contain carbon-carbon multiple bonds and branched chains as well as alicyclic and heterocyclic groups;

Q is H or OH;

- 15  $R_1$  and  $R_2$  can be either the same or different and are chosen from hydrogen or the residue of an aromatic group as listed in Scheme 1:

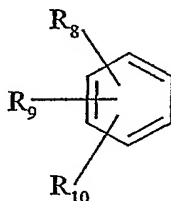
**Scheme 1**



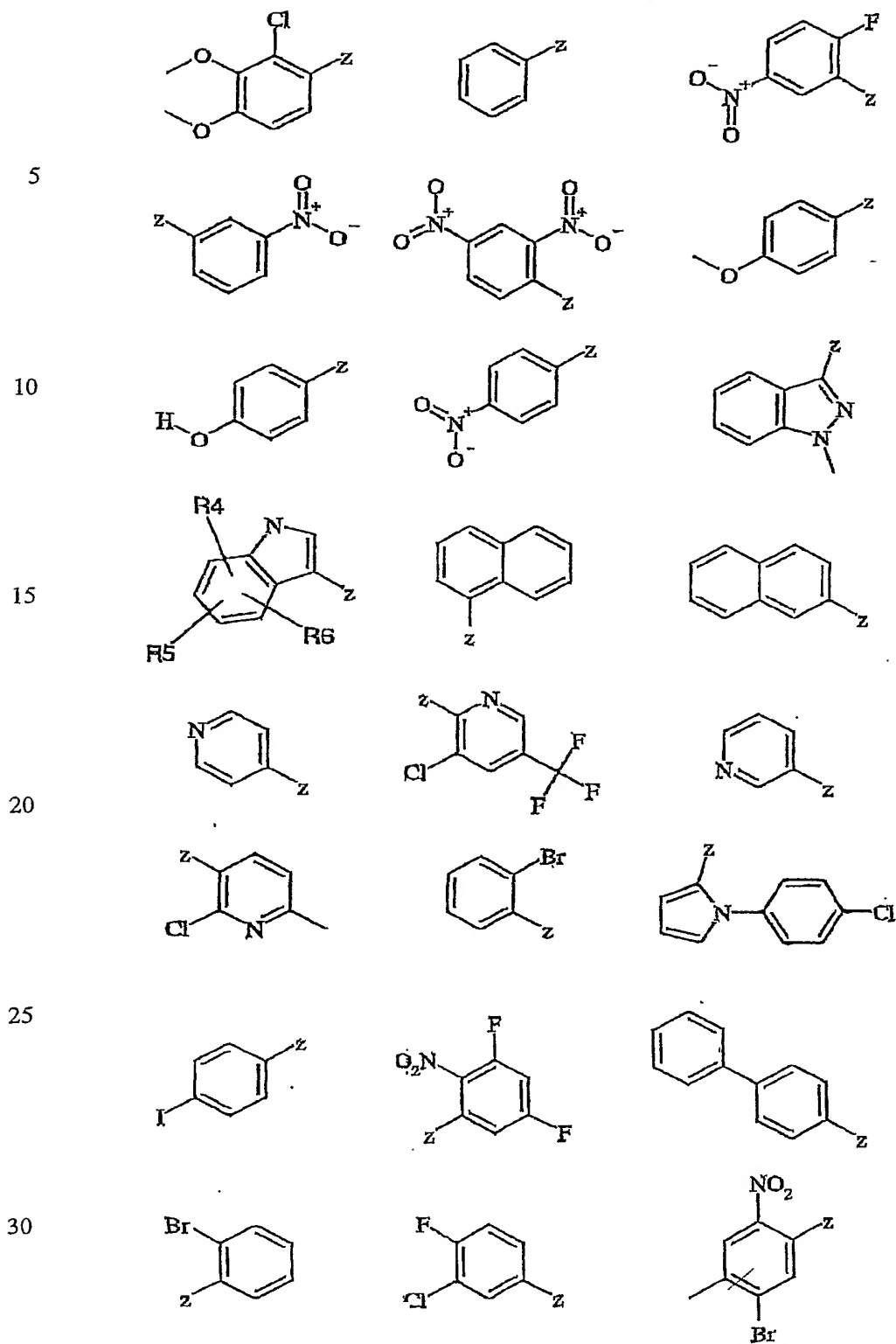
- 20 wherein  $R_4$ ,  $R_5$ ,  $R_6$ , and  $R_7$  are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon



atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho, or be selected from;

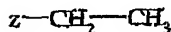
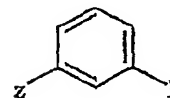
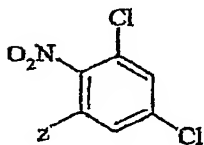
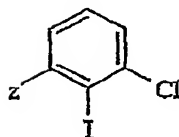
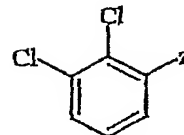
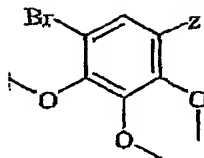
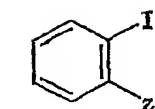


- 5 wherein R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 8 carbon atoms, electron donor groups such as alkoxy having 1 to 5 carbon atoms, which with another substituent group may form part of a ring, hydroxy or an amine (primary, secondary or tertiary) having 0, 1 or 2 carbon atoms, electron accepting groups such as cyano, nitro, trifluoroalkyl, amide or sulpho;
- 10 with the proviso that where X is (CH<sub>2</sub>)<sub>n</sub> and n is 0, R<sub>2</sub> is not H;  
or a pharmacologically active salt thereof,  
for the treatment of conditions associated with the melanocortin receptors.
- 15 2. Use according to claim 1, wherein one or more of R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>10</sub> are alkyl having 1 to 8 carbon atoms.
3. Use according to claim 2, wherein the alkyl is methyl or ethyl.
- 20 4. Use according to any one of the previous claims, wherein one or more of R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>10</sub> are alkoxy.
5. Use according to claim 4, wherein the alkoxy is methoxy.
- 25 6. Use according to any one of the previous claims wherein one or more of R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub>, and R<sub>10</sub> are halogen atoms.
7. A compound of the general formula (I) as defined in claim 1, wherein R<sub>1</sub> and R<sub>2</sub> are selected from



26

5



- 10 wherein  $z$  denotes the point of attachment;  
or a pharmacologically active salt thereof;  
with the proviso that:  
when  $R_1$  is a phenyl,  $R_2$  must be selected from a different substituent than phenyl;  
when  $R_1$  is 4-methoxyphenyl,  $R_2$  must be selected from a different substituent than 4-  
15 methoxyphenyl and 1,3-dinitrophenyl;  
when  $R_2$  is 4-methoxyphenyl,  $R_1$  must be selected from a different substituent than 4-  
methoxyphenyl; and  
when  $R_2$  is methyl,  $R_1$  must be selected from a substituent different than phenyl.

- 20 8. A compound selected from

25

30

No.	Name
1	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-benzylguanidine
2	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-phenylguanidine
3	N-(2-Fluoro-5-Nitrobenzylideneamino) N'-hydroxy-N''-phenylguanidine
4	N-(3-nitrobenzylideneamino)-N'-hydroxy-N''-phenylguanidine
5	N-(2,4-dinitrobenzylideneamino)-N'-hydroxy-N''-phenylguanidine
6	N-(2-fluoro-5-nitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine
7	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-hydroxy-N''-methylguanidine
8	N-(3-nitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine
9	N-(2,4-dinitrobenzylideneamino)-N'-hydroxy-N''-methylguanidine
10	N-(4-methoxybenzylideneamino)-N'-(2-phenylethyl)guanidine
11	N-(pyrid-4-yl-methylideneamino)-N'-(naphthalen-1-yl-methyl)guanidine
12	N-(1H-indol-3-ylmethylideneamino)-N'-(2-phenylethyl)guanidine
13	N-(1H-indol-3-yl-methylideneamino)-N-(naphthalen-1-ylmethyl)guanidine

5	15	N-(pyrid-4-yl-methylideneamino)-N'-[2-(1H-indol-3-yl-ethyl)]guanidine	121-123
	16	N-(2-chloro-3,4-dimethoxybenzylideneamino)-N'-phenylguanidine	179-181
	17	N-(2-fluoro-5-nitrobenzylideneamino)-N'-phenylguanidine	191-193
	18	N-(4-hydroxybenzylideneamino)-N'-benzylguanidine	192-194
	19	N-(2,4-dinitrobenzylideneamino)-N'-phenylguanidine	180-190
10	20	N-(4-nitrobenzylideneamino)-N'-(2-phenylethyl)guanidine	241-243
	21	N-(naphthalen-2-yl-methylideneamino)-N'-(2-phenylethyl)guanidine	244-246
	22	N-(naphthalen-2-yl-methylideneamino)-N'-benzylguanidine	242-244
	23	N-(naphthalen-2-yl-methylideneamino)-N'-naphthalen-2-ylguanidine	218-220
	24	N-(4-Nitrobenzylideneamino)-N'-benzylguanidine	239-241
15	25	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(pyrid-3-ylmethyl) guanidine	58-60
	26	N-(2-chloro-6-methyl-pyrid-3-ylmethylideneamino)-N'-(pyrid-3-ylmethyl)guanidine	227-228
	27	N-(2-Bromobenzylideneamino)-N'-phenethylguanidine	154-155
	28	N-(2-Bromobenzylideneamino)-N'-phenylguanidine	149-152
	29	N-[1-(4-Chlorophenyl) 1H-Pyrrol-2-ylmethyleneamino]-N'-benzylguanidine	190-192
20	30	N,N'-Di-(naphthalen-1-ylmethyleneamino)guanidine	253-255
	31	N,N'-Di-(2-Bromobenzylideneamino)guanidine	268-270
	32	N,N'-Di-(2-Chloro-3,4-Dimethoxybenzylideneamino)guanidine	228-230
	33	(3-Phenyl-allylideneamino)-N'-2-phenylethyl)guanidine	175-177
	34	N,N'-Di-(1-(4-Chlorophenyl)-1H-pyrrol-2-ylmethyleneamino)guanidine	221-223
25	35	N-(2-Fluoro-5-nitrobenzylideneamino)-N'-methylguanidine	217-219
	36	N-(Indol-3-ylmethylenimino)-N'-(1-methylindazol-3-ylmethyl)guanidine	foam
	37	N-(2-Chloro-3,4-dimethoxybenzylideneamino)-N'-methylguanidine	207-210
	38	N-(indol-3-ylethylideneamino)-N'-(indol-3-ylethyl) guanidine	
	39	N-(indol-3-ylmethylideneamino)-N'-indol-3-ylguanidine	
30	40	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N'-(N''-methyl-2-azaindol-3-yl-methyl)guanidine	
	41	N-(indol-3-yl-methylideneamino)-N'-(N''-methyl-2-azaindol-3-yl-methyl)guanidine	
	42	N-(indol-3-yl-butylideneamino)-N'-(N''-methyl-2-azaindol-3-yl-methyl)guanidine	
	43	N-(1-methyl-indol-3-yl-methylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
	44	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
	45	N-(indol-3-ylmethylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	
	46	N-(indol-3-ylbutylideneamino)-N'-(2-methyl-5-methoxy-indol-3-ylethyl) guanidine	

47	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N'-(indol-3-ylmethyl) guanidine	
48	N-(2-methyl-5-methoxy-indol-3-yl-ethylideneamino)-N'-(indol-3-ylmethyl)guanidine	
49	N-(indol-3-ylmethylideneamino)-N'-(indol-3-ylmethyl) guanidine	
50	N-(indol-3-ylbutylideneamino)-N'-(indol-3-ylmethyl) guanidine	
51	N-(1-methyl-2-azaindol-3-ylmethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
52	N-(2-methyl-5-methoxy-indol-3-ylethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
53	N-(indol-3-ylmethylideneamino)-N'-(indol-3-ylbutyl) guanidine	
54	N-(indol-3-ylbutylideneamino)-N'-(indol-3-ylbutyl) guanidine	
55	N-(2-methyl-indol-3-ylethylideneamino)-N'-(2-methyl-indol-3-ylethyl)guanidine	
56	N-(pyrid-3-ylpropylideneamino)-N'-(pyrid-3-ylpropyl) guanidine	
62	N-(pyrid-3-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl)guanidine	
64	N-(2-chloro-6-methyl-pyrid-3-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
65	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(2-chloro-6-methyl-pyrid-3-ylmethyl) guanidine	
66	N-(pyrid-3-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethyl) guanidine	
68	N-(3-chloro-5-methyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
69	N-(3-chloro-5-trifluoromethyl-pyrid-2-ylmethylideneamino)-N'-(3-chloro-5-trifluoromethyl-pyrid-2-yl) guanidine	
70	N-(2-ethoxy-pyrid-3-ylmethylideneamino)-N'-(2-ethoxy-pyrid-3-ylmethyl)guanidine	
71	N-(pyrrol-2-ylmethylideneamino)-N'-(pyrrol-2-ylmethyl) Guanidine	
72	N-(3-nitrobenzylideneamino)-N'-phenylguanidine	
73	N-(3-nitrobenzylideneamino)-N'-methylguanidine	
74	N-(2,4-dinitrobenzylideneamino)-N'-methylguanidine	
75	N-(3,5-Difluoro-2-nitrobenzylideneamino)-N'-(4-Iodobenzyl)guanidine	
76	N-(2-Bromobenzylideneamino)-N'-[2-(4-Biphenyl)-Ethyl]guanidine	
77	N-(3-Chloro-4-Fluorobenzylideneamino)-N'-[2-(3-Chloro-4-Fluorophenyl)ethyl]guanidine	
78	N-(4-Phenylbenzylideneamino)-N'-(5-Bromo-4-Methyl-2-Nitrobenzyl)guanidine	
79	N-(4-Phenylbenzylideneamino)-N'-(2-[2-Iodophenyl)ethyl]guanidine	
80	N-(3-Chloro-4-fluorobenzylideneamino)-N'-(2,3,4-trimethoxy-5-bromobenzyl)guanidine	
81	N-(3-Chloro-2-iodobenzylideneamino)-N'-(2,3-Dichlorobenzyl)guanidine	
82	N-(3,5-Dichloro-2-nitrobenzylideneamino)-N'-[2-(3,5-difluoro-2-nitrophenyl)ethyl]guanidine	

5 or a pharmacologically acceptable salt thereof.

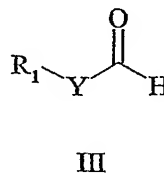
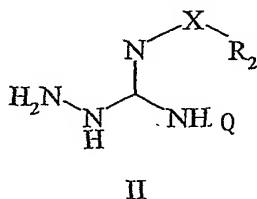
9. A compound as claimed in claim 7 or 8 which additionally comprises a label, preferably a radioactive label, or a toxic agent.

10. A prodrug from which a compound as claimed in any one of claims 7 to 9 is formed *in vivo*.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 7 to 9 or a prodrug as claimed in claim 10, together with one or more adjuvants, carriers or excipients.

12. A compound as claimed in any one of claims 7 to 10 for use as a medicament.

13. A process for the production of a compound as claimed in claim 1 which comprises reacting a guanidine derivative of formula (II) with an aldehyde of formula (III).



wherein X, Y, Q, R<sub>1</sub> and R<sub>2</sub> are as defined in claim 1.

14. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of inflammation

15. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 11 in the production of a medicament for the treatment of mental disorders.
- 5 16. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of disfunctions of the endocrine system or an hormonal system.
- 10 17. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of sexual functions and/or sexual dysfunctions.
- 15 18. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of drug-induced or other disorders of the blood and/or lymphoid system.
- 20 19. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of allergic disorders.
- 20 20. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of disorders of the cardiovascular system.
- 25 21. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of pain.
- 30 22. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for inducing skin tanning or for inducing lighter skin colour.

23. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of diabetes type II.
- 5 24. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of obesity.
25. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for the treatment of anorexic  
10 conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions.
26. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for inducing peripheral nerve  
15 regeneration.
27. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10 in the production of a medicament for inducing central nerve  
20 regeneration.
28. A method of treatment inflammation comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 25 29. A method of treatment mental disorders comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 30 30. A method of treating dysfunctions of the endocrine system or an hormonal system comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.



31. A method of treating sexual functions and/or sexual dysfunctions comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 5 32. A method of treating drug-induced disorders of the blood and/or lymphoid system comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 10 33. A method of treating disorders of the cardiovascular system comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 15 34. A method of treating pain comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
35. A method of inducing skin tanning or for inducing lighter skin colour comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 20 36. A method of treating diabetes type II comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 25 37. A method of treating obesity comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 30 38. A method of treating anorexic conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.

39. A method of inducing peripheral nerve regeneration comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 5 40. A method of inducing central nerve regeneration comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 10 41. Use of a compound as claimed in any one of claims 1 to 9 or a prodrug as defined or claimed in claim 10 in the production of a medicament for the treatment of skin disorders including for the treatment of melanoma.
- 15 42. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as defined or claimed in claim 10 in the production of a medicament for the treatment and/or diagnosis of malignancies, such as melanoma and metastases.
- 20 43. A method of treating a skin disorder, including the treatment of melanoma, comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 25 44. A method of treating and/or diagnosing malignancies, such as melanoma and metastases, comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.
- 30 45. Use of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as defined or claimed in claim 10 in the production of a medicament for the treatment of ischemia and/or ischemia/reperfusion.
46. A method of treating ischemia and/or ischemia/reperfusion comprising the use or administration of a compound as defined or claimed in any one of claims 1 to 9 or a prodrug as claimed in claim 10.

## INTERNATIONAL SEARCH REPORT

Interj	al Application No
PC	: 01/03556

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C281/18 C07D213/36 C07D209/14 C07D207/335 A61K31/155  
A61K31/40 A61K31/44 A61P25/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	- WILLIAM O. FOYE ET AL.: "Synthesis and Biological Activity of Guanyldrazones of 2- and 4-Pyridine and 4-Quinoline Carboxaldehydes" JOURNAL OF PHARMACEUTICAL SCIENCES., vol. 79, no. 6, June 1990 (1990-06), pages 527-530, XP002180467 AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON., US ISSN: 0022-3549 page 528 -page 529; examples 14,16 page 530, column 1, line 28 -column 2, line 35	7,11,13
A	WO 99 64002 A (MERCK) 16 December 1999 (1999-12-16) cited in the application claims; examples	1,7,11, 12,14-46
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

18 October 2001

Date of mailing of the international search report

31/10/2001

Name and mailing address of the ISA

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Authorized officer

Zervas, B

## INTERNATIONAL SEARCH REPORT

Inter	al Application No
PC	3 01/03556

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 35952 A (MELACURE THERAPEUTICS) 22 June 2000 (2000-06-22) page 58, line 34 -page 59, line 10; claims -----	1,7,11, 12,14-46

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7,9,11-46 (all in part); 10 (not searched)

1. Present claims 7 and 9 - 13 relate to an extremely large number of possible compounds and to their preparation. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of the general formula (I) as defined in claim 7, wherein X and Y represent independently  $(CH_2)_n$ , where n is 0, 1, 2, 3, 4, 5 and to the compounds claimed in claim 8.

2. The scope of claims 10 - 46, in as far as the expression "prodrug" is concerned, is so unclear that a meaningful international search is impossible with regard to this expression.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/JP 01/03556

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9964002	A	16-12-1999	AU 4680199 A	30-12-1999
			EP 1085869 A1	28-03-2001
			WO 9964002 A1	16-12-1999
			US 6294534 B1	25-09-2001
			US 2001029259 A1	11-10-2001
<hr/>				
WO 0035952	A	22-06-2000	AU 1789900 A	03-07-2000
			WO 0035952 A2	22-06-2000
<hr/>				